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(54) Title: THE USE OF A BENZENESULFONAMIDE COMPOUND IN THE TREATMENT OF OBESITY

(57) Abstract: The invention relates to a novel method of medical treatment, in particular the treatment of obesity.

THE USE OF A BENZENESULFONAMIDE COMPOUND IN THE TREATMENT OF OBESITY

The present invention relates to the use of a known 5-HT_6 receptor antagonist in the treatment of obesity.

Obesity is a chronic disease believed to have a familial component. It is characterised by the tendency to increase weight as a consequence of a combination of lack of physical exercise and an abundance of high-fat foods. Obesity increases ones risk of developing conditions such as high blood pressure, diabetes, heart disease, stroke, gall bladder disease and cancer of the breast, prostate and colon. Obesity is a disease that affects at least 39 million Americans (more than one quarter adults and about one in five children). Each year, obesity causes at least 300,00 excess deaths in the US and costs the country more than $100 billion.

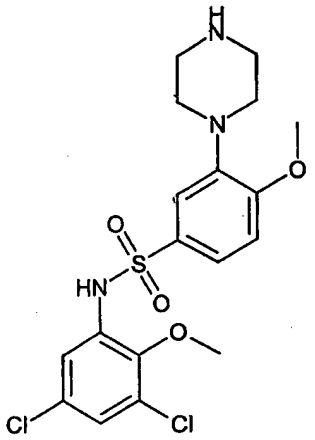
The American Obesity Association believe the most effective treatment for obesity to be a combination of behaviour therapy (eg. improved diet and increased physical activity) and drug therapy. Several drugs have been approved by the US Food and Drug Administration for obesity which either work as appetite suppressants or by blocking the absorption of dietary fat. However, some treatments have been associated with adverse health effects, such as the combination drug therapy of fenfluramine and phentermine.

WO 02/08179 (Biovitrum AB) discloses a series of aryl sulfonamides as serotonin antagonists for the treatment of obesity, disclosing specifically 5-HT_6 receptor antagonists previously disclosed in WO 98/27081 and WO 99/42465 (SmithKline Beecham plc).

International patent application PCT/EP01/09927 describes a novel sulfonamide compound, *N*-(3,5-dichloro-2-methoxy-phenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide, as a potent 5-HT_6 receptor antagonist. This compound is disclosed in PCT/EP01/09927 as being of potential use in the treatment or prophylaxis of certain CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, cognitive memory disorders (e.g. Alzheimers disease, age related cognitive decline and mild cognitive impairment), Parkinsons Disease, ADHD (Attention Deficit Disorder/Hyperactivity Syndrome), sleep disorders (including disturbances of Circadian rhythm), feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, disorders associated with spinal trauma and/or head injury such as hydrocephalus and certain GI (gastrointestinal) disorders such as IBS (Irritable Bowel Syndrome). Furthermore, PCT/EP01/09927 indicates that this compound is of particular use in the treatment of Alzheimers disease, age related cognitive decline, ADHD, depression and/or anxiety.

We have found that *N*-(3,5-dichloro-2-methoxy-phenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide has demonstrated appetite suppressant effects as confirmed by the data enclosed herein therefore confirming the potential of this compound in the treatment of obesity.

The present invention therefore provides, in a first aspect, the use of *N*-(3,5-dichloro-2-methoxy-phenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide, the compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of obesity.

The compound of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in J. Pharm. Sci., 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid.
Preferably, the compound of formula (I) is used as the hydrochloride or the p-toluenesulfonate salt.
The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The compound of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates as well as a compound containing variable amounts of water.

The present invention further provides a method of treatment of obesity which comprises administering to a host in need thereof an effective amount of the compound of formula (I) or a pharmaceutically acceptable salt thereof.

When used in therapy, the compound of formula (I) is usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

Thus, the present invention further provides a pharmaceutical composition for use in the treatment of obesity which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 1 to 1000 mg, more suitably 5 to 600 mg, for example 5 to 300 mg; and such unit doses may be administered more than once a day, for example two or three times a day, so that the total daily dosage is in the range of about 5 to 1000 mg; and such therapy may extend for a number of weeks or months.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The invention is illustrated by the following Examples:

Description 1

1-(2-Methoxyphenyl)-4-trichloroacetylpiperazine (D1)

A solution of 1-(2-methoxyphenyl)piperazine (7.0g) in dichloromethane (30ml) was added over 0.25h to a stirred solution of trichloroacetyl chloride (4.06ml) in dichloromethane (40ml) at room temperature under argon. Diisopropylethylamine (5.95ml) was then added and the whole was stirred for 18h. The reaction mixture was washed with water (2 x 100ml), dried (Na_2SO_4) and concentrated to give the title compound (D1) as an oil (11.2g, 91%), MS: m/z (MH^+) 337/339.

Description 2

3-(4-Trichloroacetylpiperazin-1-yl)-4-methoxybenzenesulfonyl chloride (D2)

A solution of 1-(2-methoxyphenyl)-4-trichloroacetylpiperazine (D1) (10g) in dichloromethane (115ml) was added over 0.3h to ice-cooled chlorosulfonic acid (52ml). After 0.5h at 0°C then 1 hour at room temperature, the solution was poured onto a mixture of ice-water (500g) and dichloromethane (500ml) with rapid stirring. The layers were separated and the organic phase was washed with water (2 x 800ml), dried ($MgSO_4$) and concentrated to give the title compound (D2) as a foam (6g, 46%), MS: m/z (MH^+) 435/437.

Description 3

1,5-Dichloro-2-methoxy-3-nitro benzene (D3)

A stirred suspension of potassium carbonate (99.7g), iodomethane (89ml) and 2,4-dichloro-6-nitrophenol (containing 20% water)(100g) in *N,N*-dimethylformamide (1L) was heated at 60°C for 18h. The reaction mixture was cooled and the solid was filtered-off and washed with dichloromethane (2 x 500ml). The filtrate was evaporated *in vacuo* to an oily solid which was taken-up in dichloromethane (1.5L). The combined organics were washed with 1M sodium hydroxide (1.5L), then water (1L). The organic phase was dried ($MgSO_4$) and concentrated to give the title compound (D3) as a solid (35.7g, 42%). MS: m/z ($M-H^-$) 221/223.

Description 4

3,5-Dichloro-2-methoxy-phenylamine (D4)

A vigorously stirred suspension of iron powder (42.5g), 1,5-dichloro-2-methoxy-3-nitro benzene (D3) (65g) in methanol (500ml) and saturated aqueous ammonium chloride solution (700ml) was heated at reflux for 3h. The mixture was filtered and the solid washed with dichloromethane/methanol (1:1) (4 x 150ml) then dichloromethane (4 x 200ml). The filtrate was diluted with water (500ml), shaken and the layers separated. The aqueous layer was further extracted with dichloromethane (500ml) and the combined organic extracts were dried ($Mg SO_4$) and concentrated to an oil. The oil was purified by column chromatography on silica eluting with dichloromethane/hexane (4:1) then dichloromethane to afford the title compound (D4) as an oil (41.8g, 74%). MS: m/z (M^+) 191/192.

Description 5

***N*-(3,5-Dichloro-2-methoxy-phenyl)-4-methoxy-3-[4-(2,2,2-trichloro-ethanoyl)-piperazin-1-yl]-benzenesulfonamide (D5)**

A solution of 3,5-dichloro-2-methoxy-phenylamine (D4) (41g), 3-(4-trichloroacetylpiperazin-1-yl)-4-methoxybenzenesulfonyl chloride (D2)(93g) and dry pyridine (51.7ml) in dry 1,2-dichloroethane (1.5L) was refluxed for 40h under argon. The reaction mixture was cooled to room temperature and washed with 1M hydrochloric acid (1.5L), water (2x1.5L), dried ($MgSO_4$) and concentrated *in vacuo* to an oil. The oil was stirred with hot ethanol (400ml) to give the title compound (D5) as a cream solid which was filtered and washed with cold ethanol then diethyl ether (104.8g, 83%).
^1H (400MHz, $CDCl_3$) δ 1.84-1.87 (2H, m), 3.08-3.10 (4H,m), 3.64 (3H, s), 3.73-3.76 (2H, m), 3.93 (3H, s), 6.91 (1H, d, J 8.4Hz), 7.04 (1H, d, J 2.4Hz), 7.14 (1H, s), 7.30 (1H, d, J 2.4Hz), 7.53-7.57 (2H, m); MS: m/z (MH^+) 590/592/594.

The compound D2 can also be obtained by the following procedure:

Description 2a

3-(4-Trichloroacetylpiperazin-1-yl)-4-methoxybenzenesulfonyl chloride (D2a) - alternative procedure to D1/D2

1-(2-methoxyphenyl)piperazine hydrochloride was treated with trichloroacetyl chloride (2.04eq), added portionwise, in dichloromethane solution in the presence of diisopropylethylamine (1.02 eq). The mixture was stirred at 20 to 22°C for 30 minutes at which point the reaction was shown to be complete by HPLC analysis. The resulting reaction mixture was washed with water, then the aqueous phase back extracted with dichloromethane. The combined organic phases were washed with water then dried over sodium sulfate and filtered through Celite (Diatomaceous Earth). The filtrate was added to chlorosulfonic acid over 100 minutes at -9 to 13°C then stirred at 13 to 21°C for 17.5 hours. The resulting solution was then added to a pre-cooled (1°C) mixture of dichloromethane and process water over *ca.* 2.5 hours at 0 to 18°C. The phases were separated and the aqueous phase was extracted with dichloromethane then the combined organic phases washed with water. After clarification through an in-line filter the organic solution was heated to reflux and dichloromethane exchanged for toluene by put-and-take distillation. The toluene solution was then cooled to 18°C. and diluted with *n*-heptane to precipitate the product, which was collected by centrifugation and dried to give the title compound.

The compound D4 can also be obtained by the following procedure.

Description 4a

3,5-Dichloro-2-methoxy-phenylamine (D4a) - alternative procedure to D3/D4

2,4-dichloro-6-nitrophenol was dissolved in DMF and treated with dimethylsulfate (3.3eq), added over 55 minutes, in the presence of potassium carbonate (~2.8eq), then stirred at 35 - 40°C for 3 hours. The mixture was cooled to 25°C then partitioned between *n*-heptane and aqueous ammonia. The lower aqueous layer was re-extracted with *n*-heptane then the two organic layers were combined and washed sequentially with 10% aqueous potassium carbonate solution and water. The organic solution was then hydrogenated over 1% platinum on carbon, type 156, 50% paste at 15 - 25°C and 40 - 47 psig hydrogen until the reaction was shown to be complete by HPLC. The mixture was filtered through Celite (Diatomaceous Earth) then evaporated to dryness under reduced pressure at to give the title compound as an oil.

The compound D5 can also be obtained by the following procedure.

Description 5a

N-(3,5-Dichloro-2-methoxy-phenyl)-4-methoxy-3-[4-(2,2,2-trichloro-ethanoyl)-piperazin-1-yl]-benzenesulfonamide (D5a) - alternative procedure to D5

3-(4-Trichloroacetylpiperazin-1-yl)-4-methoxybenzenesulfonyl chloride (D2)(1.0 equiv) was suspended in dichloromethane (0.9 vols) with stirring and 3,5-Dichloro-2-methoxy-phenylamine (D4) (1.05 equiv) added. A solution of isoquinoline (1.5 equiv) in dichloromethane (0.2 vols) was added in four portions maintaining the temperature between 17 and 26°C. The mixture was heated to reflux for 2 hours 15 minutes. The solvent was exchanged for ethanol (3.9vols) by put and take distillation. The suspension was cooled to 0 to 5°C and stirred for 1 hour. The title product was isolated by filtration, washed with ethanol (1.5 vols) and dried at 30 to 35°C under vacuum

Example 1

***N*-(3,5-Dichloro-2-methoxy-phenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide (E1)**

A 1M solution of potassium hydroxide (609ml) was added over 5 minutes to a rapidly stirred solution of *N*-(3,5-dichloro-2-methoxy-phenyl)-4-methoxy-3-[4-(2,2,2-trichloro-ethanoyl)-piperazin-1-yl]-benzenesulfonamide (D5)(103g) in tetrahydrofuran (1.5L) at room temperature. After stirring for 18h, the stirred, ice-cooled mixture was adjusted to pH 7.0 by the addition of concentrated hydrochloric acid to afford the title compound (E1) as a cream solid which was filtered, washed with water (3 x 100ml) and dried (72.9g, 94%).

^{1}H (400MHz, DMSO-D_6/CD_3OD 4:1) δ2.95-3.15 (8H, m), 3.63 (3H, s), 3.82 (3H, s), 6.88 (1H, br d), 7.0 (1H, br dd), 7.18 (1H, br d), 7.29 (1H, br d), 7.40 (1H, br dd); MS: m/z (MH^+) 446/448. m.p. 189-90°C.

Example 2

***N*-(3,5-Dichloro-2-methoxy-phenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide Hydrochloride (E2)**

N-(3,5-Dichloro-2-methoxy-phenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide (E1) (20g) was suspended in ethanol (200ml) at room temperature and to the stirred suspension was added conc. hydrochloric acid (density = 1.18, 4.3ml, 1.1 equivalents) over 1 minute. The resulting solution was left to stand for 24h at 0°C to give the title compound (E2) as a white solid (16.4g, 76%).

^{1}H (400MHz, DMSO-d_6) δ 3.18 (8H, br s), 3.53 (3H, s), 3.86 (3H, s), 7.12 (1H, d, J 8.4Hz), 7.32 (1H, d, J 2.4Hz), 7.36 (1H, d, J 2.4Hz), 7.40 (1H, d, J 2.4Hz), 7.46 (1H, dd, J 2.4, 8.4Hz), 9.4 (2H, br s), 10.0 (1H, br s); MS: m/z (MH^+) 446/448. m.p. 207-9°C.

Example 3

***N*-(3,5-Dichloro-2-methoxyphenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide 4-toluenesulfonate (E3)**

A solution of 4-toluenesulfonic acid monohydrate (10.7g, 56mmole) in ethanol (75ml) was added to a stirred suspension of *N*-(3,5-dichloro-2-methoxyphenyl)-4-methoxy-3-piperazin-1-yl-

benzenesulfonamide (E1) (25g, 56mmole) in ethanol (400ml) at reflux. The resulting clear pale yellow solution was then allowed to cool with stirring. The solid product was collected by filtration and dried at ambient temperature and reduced pressure to constant weight to give the title compound (E3) as a white crystalline solid (28g, 81%).

^{1}H NMR (400MHz, DMSO-d_6): δ2.29 (3H, s), 3.13 (4H, br s), 3.36 (4H, br s), 3.53 (3H, s), 3.86 (3H, s), 7.12 (3H, m), 7.33 (1H, d, J 2.4Hz), 7.37 (2H, m), 7.48 (3H, m), 8.68 (1H, br s), 10.12 (1H, s).m.p. 207-209°C.

Example 4

Appetite suppressant effects of *N*-(3,5-dichloro-2-methoxy-phenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide hydrochloride during 10 day dog study

Groups consisting of 1 male and 1 female beagle dog were administered an oral dose of *N*-(3,5-dichloro-2-methoxy-phenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide hydrochloride (E2) in gelatin capsules at 30 mg/kg/day for 8 days. On Day 9, the dose administered was reduced from 30 to 20 mg/kg/day and the dosing period extended to Day 13 to assess the effects of E2 at the lower dose.

The results demonstrated that when dosed at 30mg/kg/day, food consumption was reduced to 63% and 91% of baseline consumption on day 3 in males and females, respectively. Over the next 5 days, further reductions ranged from 48 to 27% (for males) and 86 to 12% (for females) of baseline values. This result correlated with an observation of body weight loss seen between days 1 and 9 of treatment. Following the reduction of the dose on day 9 to 20 mg/kg/day, this lower dose being administered for a further 5 day period, food consumption increased to 63% and 42% (of baseline consumption) in male and female animals, respectively.

Example 5

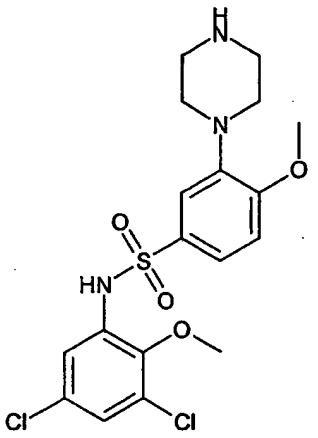
Appetite suppressant effects of *N*-(3,5-dichloro-2-methoxy-phenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide 4-toluenesulfonate during 28 day dog study

Groups consisting of 3 Male and 3 female beagle dogs were dosed with *N*-(3,5-dichloro-2-methoxy-phenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide 4-toluenesulfonate (E3) once daily at 20 mg/kg/day in gelatin capsules for 28 or 29 days. Due to high level reductions in food consumption and associated body weight loss, the dose was lowered to 15 mg/kg/day of E3 from Day 11 following a 2-day treatment-free period.

The results showed that up to 12% body weight loss was observed in most animals dosed at 20/15mg/kg/day over the treatment period. During the treatment-free period, animals either recovered the lost weight or maintained their current weight (which was associated with normal food consumption). All animals given 20/15 mg/kg/day exhibited a reduction in food consumption (total inappetance or low intakes of <50% of food) throughout the first week of treatment when food was available for 5 hours. Normal food consumption was seen during the treatment-free period.

CLAIMS:

1. Use of *N*-(3,5-dichloro-2-methoxy-phenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide, the compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of obesity.

2. Use according to claim 1 wherein said compound of formula (I) is *N*-(3,5-dichloro-2-methoxy-phenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide hydrochloride or *N*-(3,5-dichloro-2-methoxy-phenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide tosylate.

3. A method of treatment of obesity which comprises administering to a host in need thereof an effective amount of *N*-(3,5-dichloro-2-methoxy-phenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide, the compound of formula (I) or a pharmaceutically acceptable salt thereof.

4. A method according to claim 3 wherein said compound of formula (I) is *N*-(3,5-dichloro-2-methoxy-phenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide hydrochloride or *N*-(3,5-dichloro-2-methoxy-phenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide tosylate.

5. A pharmaceutical composition for use in the treatment of obesity which comprises *N*-(3,5-dichloro-2-methoxy-phenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide, the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

6. A pharmaceutical composition according to claim 5 wherein said compound of formula (I) is *N*-(3,5-dichloro-2-methoxy-phenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide hydrochloride or *N*-(3,5-dichloro-2-methoxy-phenyl)-4-methoxy-3-piperazin-1-yl-benzenesulfonamide tosylate.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/02039

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P3/04 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 02 18358 A (BROMIDGE STEVEN MARK ;MOSS STEPHEN FREDERICK (GB); SMITHKLINE BEEC) 7 March 2002 (2002-03-07) the whole document	5,6
P,A	WO 02 100822 A (JENMALM JENSEN ANNIKA ;MOTT ANDREW (SE); THOR MARKUS (SE); BIOVITR) 19 December 2002 (2002-12-19) page 3, line 10 - line 18 claims 1,16-24	1-6
A	US 6 316 450 B1 (BROMIDGE STEVEN MARK ET AL) 13 November 2001 (2001-11-13) column 8, line 46 - line 58; claims	1-6

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
16 June 2003	27/06/2003

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